SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Axhidrox pump-pack 2.2 mg/pump actuation cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Glycopyrronium

1 g cream contains glycopyrronium bromide, equivalent to 8 mg of glycopyrronium. One actuation of the pump delivers 270 mg cream, which contains glycopyrronium bromide, corresponding to 2.2 mg glycopyrronium.

Excipients with known effect

This medicine contains 21.6 mg cetostearyl alcohol, 2.7 mg benzyl alcohol and 8.1 mg propylene glycol per pump actuation.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream

White glossy cream

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Axhidrox is indicated for the topical treatment of severe primary axillary hyperhidrosis in adults.

4.2 Posology and method of administration

Cutaneous use

Axhidrox is for topical use in the underarm area only and not for use in other body areas.

Posology

The recommended dosage of Axhidrox is two pump actuations per armpit (equivalent to 540 mg of cream or 4.4 mg glycopyrronium per armpit). After priming, the pump must be pressed down all the way twice to get the desired dose of 540 mg cream (4.4 mg glycopyrronium).

During the first 4 weeks of treatment, Axhidrox is applied to each armpit evenly, once a day, preferably in the evening.

From the 5th week on, the frequency of application of Axhidrox may be reduced to twice a week, depending on the reduction of axillary sweating.

Continuous treatment of primary axillary hyperhidrosis with Axhidrox is required to maintain the effect.

Paediatric population

The safety and efficacy of Axhidrox in children and adolescents under 18 years has not yet been established.

No data are available.

Elderly

The safety and efficacy of Axhidrox in the elderly population above 65 years has not been established.

Renal impairment

Axhidrox can be used at the recommended dose in patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis Axhidrox should be used only if the expected benefit outweighs the potential risk since the systemic exposure to glycopyrronium may be increased in this population (see section 4.4).

Hepatic impairment

No studies have been conducted in patients with hepatic impairment. Glycopyrronium is predominantly cleared by renal excretion and therefore no major increase in exposure to the active substance is to be expected in patients with hepatic impairment.

No dose adjustment is required in patients with hepatic impairment.

Method of administration

Preparation of the pump before the first use

The multidose container requires priming before it is used for the first time.

To get a full initial dose, the air trapped in the pump must be removed as follows:

- Hold the pump at an angle (see illustration) and repeatedly press the pump down until cream comes out of the opening onto a piece of paper.
- Slowly push the pump down fully another 10 times and put the pumped cream onto the paper. Dispose the paper with the dispensed cream via waste bin only.
- The pump is now ready for use. Repeated preparation of the pump is not necessary for subsequent use.

Regular application of the cream

After priming, the application of the cream is done using the cap as further detailed:

- Hold the pump in one hand with the opening of the pump towards the removed cap of the pump (see illustration).
- Fully press the pump twice to apply the recommended amount of cream to the top of the cap.

- Using the cap, evenly distribute the cream in one armpit.
- Repeat this process for the second armpit.
- Afterwards, for safety, wash the cap and your hands immediately and thoroughly with soap and water. This is important to avoid contact of the cream with nose, eyes or mouth as well as with other persons (see section 4.4).
- Tick off the number of treatments in the table on the outer carton (see section 6).

4.3 Contraindications

- Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.
- Medical conditions that can be exacerbated by the anticholinergic effect of Axhidrox (e.g. glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis, Sjögren syndrome).

4.4 Special warnings and precautions for use

Axhidrox should be used with caution in patients with severe prostatic hyperplasia, bladder-neck obstruction or a history or presence of urinary retention.

In these patients, doctors and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, distended bladder) and patients must be instructed to immediately discontinue the use of Axhidrox and to consult a doctor if any of these signs or symptoms develop.

In patients with severe renal impairment (estimated glomerular filtration rate below 30 ml/min/1.73 m^2), including those with end-stage renal disease requiring dialysis, Axhidrox should be used only if the expected benefit outweighs the potential risk. These patients should be monitored closely for potential adverse reactions.

Because an increased heart rate is a known effect of anticholinergics, Axhidrox should be used with caution in patients with coronary artery disease, congestive heart failure, cardiac arrhythmias and hypertension.

No studies have been performed in patients with dysfunctions of the blood-brain barrier (e.g. traumatic brain injuries within the past year, chemotherapy, radiation therapy of the head, surgery to the skull and brain, intravenous drug addicts). Axhidrox should only be used by these patients if other treatment options are not sufficiently effective.

The application of Axhidrox under the armpits should be done only with the cap of the multidose container and not with the fingers. In particular, Axhidrox must not get into the eyes (see section 4.2) since glycopyrronium can cause temporary dilation of the pupils and blurred vision. In case of contact with the mouth or nose, a reduction in the production of saliva or nasal secretions cannot be ruled out. If the eyes, nose or mouth come in contact with the cream, these areas should be rinsed immediately with plenty of water to reduce the risk of local side effects.

In order to exclude side effects, skin to skin contact of the treated skin area with other areas including skin of others should be avoided i.e. by covering the treated area with clothes (e.g. during intercourse).

If the skin of the armpits is visibly inflamed or injured this may increase the risk of local adverse reactions with Axhidrox. Therefore, Axhidrox should only be used after clinical recovery or remission of symptoms of the skin.

Since the use of Axhidrox can cause dry mouth (see section 4.8), increased risk of caries due to the reduced salivation cannot be ruled out. Careful dental hygiene and regular dental health checks are therefore recommended.

Benzyl alcohol may cause allergic reactions and mild local irritations. Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Co-administration of Axhidrox with other anticholinergic-acting medicinal products has not been studied.

It cannot be ruled out that the concomitant use of these products may result in an increase in anticholinergic effects. This applies, for example, for the use of topiramate, sedative antihistamines, tricyclic antidepressants, monoamine oxidase inhibitors, neuroleptics, antipsychotics and opioids.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of glycopyrronium bromide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on the low systemic exposure following dermal application of Axhidrox, these findings are not considered relevant for human dermal use at the approved dosing. The use of Axhidrox may be considered during pregnancy, if necessary.

Breast-feeding

Studies in lactating rats have shown that glycopyrronium and its metabolites distribute into and is enriched in milk following intravenous and oral application (for details see section 5.3).

The contact of the suckling child with the cream or Axhidrox-treated skin should be avoided, therefore a decision must be made whether to discontinue breast-feeding or to discontinue Axhidrox therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of glycopyrronium on human fertility. Animal studies have shown impaired female fertility at exposures considered in excess of the maximum human exposure, indicating low clinical relevance (see section 5.3).

4.7 Effects on ability to drive and use machines

Axhidrox has moderate influence on the ability to drive and use machines. Blurred vision, fatigue, and dizziness may occur following administration of Axhidrox (see section 4.8). Blurred vision in particular may occur if Axhidrox gets into the eyes (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse events (> 1%) were application site reactions (15.3%), dry mouth (12.3%), dry eye (3.3%), headache (1.3%), dry skin (1.3%), nasal dryness (1.5%), constipation (1.3%) and blurred vision (1.1%). While dry mouth tended to decrease with longer use, the type and frequency of all other adverse events were similar when using Axhidrox for 4 weeks as well as for 28, 52 or 72 weeks. There was no evidence that adverse events tended to get worse in severity over a longer treatment duration.

Tabulated list of adverse reactions

Adverse reactions in patients using Axhidrox up to 72 weeks are listed by MedDRA system organ class (Table 1). The table also includes data from a 14-day study with 0.5%, 1% and 2% glycopyrronium bromide (GPB) cream respectively.

Within the individual system organ classes, the adverse reactions are ranked by frequency. Within the individual frequency groups, the undesirable effects are indicated in order of decreasing severity. The frequency of adverse effects is defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Not known
Gastrointestinal disorders	Dry mouth	Constipation	Lip dry, Abdominal distension, Hard stool, Aptyalisam, Dyspepsia, Nausea	
Eye disorders		Dry eye, Vision blurred	Eye pruritus, Ocular hyperaemia, Pupils unequal, Visual impairment, Eye irritation, Mydriasis	
Respiratory, thoracic and mediastinal disorders		Nasal dryness	Oropharyngeal pain, Throat tightness, Dry throat, Nasal congestion	
Nervous system disorders		Headache	Dizziness, Somnolence, Poor quality sleep, Disturbance in attention, Head discomfort	
Psychiatric disorders			Sleep disorder, Anxiety, Restlessness	
Ear and labyrinth disorders			Vertigo	
Skin and subcutaneous tissue disorders		Dry skin	Hyperhidrosis, Pruritus, Pruritus generalized, Rash, Skin odour abnormal, Erythema, Parapsoriasis, Skin irritation, Dry hands, Dermatitis atopic, Eczema, Skin plaque, Acne, Urticaria	
General disorders and administration site conditions		Application site dermatitis, eczema, rash, papules, erythema, irritation, pain, or pruritus	Application site acne, swelling, dryness, vesicles, induration, scar or wound, Mucosal dryness, Tiredness	
Infections and infestations			Application site folliculitis, pustules	
Blood and lymphatic system disorders			Thrombocytopenia	

System organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Not known
Cardiac disorders			Tachycardia	
Immune system disorders				Hypersensitivity, Angioedema
Renal and urinary disorders			Micturition disorder	
Investigations			Electrocardiogram QT prolongation, Hepatic enzymes increased, Blood bilirubin increased and Mean cell volume increased, Mean cell haemoglobin concentration decreased	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdosage with Axhidrox is considered unlikely with topical administration to the armpits only.

If Axhidrox is misused on other parts (palms, feet, face) or large areas of the body with increased sweating an increased risk of side effects or an overdose cannot be ruled out. Signs of overdose observed especially with systemic oral administration of glycopyrronium included redness of the skin with a sensation of heat, overheating of the body, life-threatening heatstroke, dryness of the skin and mucous membranes, mydriasis with loss of accommodation, changes in mental status and fever, sinus tachycardia, a decrease in intestinal noises, functional ileus, urinary retention, hypertension, tremors and myoclonic twitching.

In case of severe or life-threatening symptoms, the administration of a quaternary ammonium anticholinesterase, such as neostigmine, should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, antihidrotics, ATC code: D11AA01

Mechanism of action

Glycopyrronium is a competitive antagonist of the muscarinic acetylcholine receptors.

Pharmacodynamic effects

Glycopyrronium inhibits acetylcholine-driven effects on smooth muscle and heart muscle cells and on various glands, including the sweat glands. In the sweat glands, this results in a reduction in perspiration.

Clinical efficacy and safety

The safety and efficacy of Axhidrox in patients with primary axillary hyperhidrosis was evaluated in a Phase 3 Study, consisting of a 4-week double-blind and placebo-controlled treatment period (Phase 3a Part), followed by an open-label extension of treatment up to 72 weeks (Phase 3b Part).

In total, 171 patients (18-65 years) were included in the 4-week, multicentre, randomized, double-blind, placebo-controlled Phase 3a Part of the pivotal study. Across the treatment groups, the mean age was 36 years, 51% were men. Almost all were of white ethnic origin. The disease severity was severe primary axillary hyperhidrosis (HDSS score of 3 or 4) with at least 50 mg of sweat production in each axilla measured gravimetrically at room temperature and at a humidity consistent with the normal climate in that area over a period of 5 minutes.

The primary endpoint was defined as the absolute change in sweat production with the GPB 1% cream vs. placebo from baseline to Day 29, as assessed by gravimetry. Key secondary endpoints were the comparison between GPB 1% cream and placebo regarding absolute change in Hyperhidrosis Quality of Life Index (HidroQoL) score from baseline to Day 29 and the percentage of responders based on HDSS score at Day 29 (improvement of $\geq$ 2 points).

After 4 weeks of treatment in the placebo-controlled Phase 3a Part, the group treated with Axhidrox showed a larger, approximately 2-fold, sweat reduction from baseline than the placebo group. The absolute reduction in sweat production from baseline to Day 29 was statistically significantly higher in the Axhidrox group compared with the placebo group (Table 2).

The analysis assessing the key secondary endpoints showed an improvement of 2 or more points in the HDSS score to treatment with Axhidrox than to treatment with placebo ($p = 0.0542$). In the analysis assessing absolute changes in the HidroQoL score, the median improvement was significantly larger in the group treated with Axhidrox than with placebo group ($p < 0.0001$).

Table 2. Data from the Phase 3a Part

	Placebo (n = 84)	**GPB 1% (n = 87)**	**GPB 1% vs. placebo p-values**
Primary endpoint			
Absolute change in sweat production from Baseline to Day 29			
Baseline [mg] (mean ± SD)	284.64 (212.47)	306.97 (249.33)	–
Change to Day 29 [mg] (mean ± SD)	–83.49 (168.21)[a]	–197.08 (252.41)[b]	0.0038
Relative change to Day 29 [%] Median (95% CI)	-34.32 (-49.71; -2.67)[a]	-64.63 (-73.13; -51.75)[b]	< 0.0001
Sweat reduction of ≥ 50%, vs baseline (number of patients, (%))	29 (34.5)	50 (57.5)	0.0114
Key secondary endpoints			
HDSS responders (≥2-point improvement from Baseline to Day 29)			
Responder rate, N (%)	10 (11.9)	20 (23.0)	0.0542
Change in the HidroQoL from Baseline to Day 29			
Total score, median (range) Change to Day 29	-1.0 (-35 - 4)[c]	-6.0 (-36 - 6)[d]	< 0.0001

HDSS = Hyperhidrosis Disease Severity Scale, HidroQoL = Hyperhidrosis Quality of Life Index, CI = confidence interval, N = number of patients, [a]N=78, [b]N=77, [c]N=79, [d]N=84.

In the open-label long-term Phase 3b Part, sweat production was significantly reduced compared to baseline 4 and 12 weeks after treatment with Axhidrox (N = 357 newly recruited patients; $p < 0.0001$ for both week 4 and 12) (Table 3).

Table 3. Data from the Phase 3b Part

Primary endpoint (only newly recruited patients)		vs. baseline
Absolute change in total sweat production assessed by GM from Baseline (Day 1b) to Week 12.		
Baseline [mg] (mean ± SD) (n = 357)	280.31 (238.24)	
Week 12 [mg] (mean ± SD) (n = 316)	123.64 (149.06)	< 0.0001
Secondary efficacy endpoints (sweat reduction):		
Sweat reduction of ≥ 50%, vs baseline (number of patients, (%)) Week 4	198 (55.5)	
Sweat reduction of ≥ 50%, vs baseline (number of patients, (%)) Week 12	193 (54.1)	
Key secondary endpoints (N=518)		
HDSS responders (≥ 2-point improvement from Baseline to Week 12) - > 25% responders		
Responders, N (%)	145 (30.8)	0.0019
HDSS responders (≥ 2-point improvement from Baseline to Week 28) - > 25% responders		
Responders, N (%)	152 (29.3)	0.0112
Absolute change in the hyperhidrosis quality of life index HidroQoL from Baseline to Week 12		
Total score Median change to Week 12 (CI)	-11.0 (-13.0; -10.0)[a]	< 0.0001

HDSS = Hyperhidrosis Disease Severity Scale, HidroQoL = Hyperhidrosis Quality of Life Index, CI = confidence interval, N = number of patients, [a]N=468

Percentage of responders (≥ 2 points improvement in HDSS) did not reach statistical significance (p = 0.0623) after 4 weeks of treatment with Axhidrox in the open-label, long-term Part of the Phase 3 Study (N = 357 patients) with Axhidrox. However, statistical significance was reached after 52 (p = 0.0072) and 72 (p < 0.0002) weeks of treatment with Axhidrox. Absolute changes in the total HidroQoL score from baseline were statistically significant on week 4, 8, 28, 52 and 72 (p < 0.0001 for all) after treatment with Axhidrox.

Patient reported outcomes, such as HDSS and HidroQoL, showed a further improvement over time despite reduction of application frequency after week 4. The hyperhidrosis symptoms ameliorated further with long-term use for up to 72 weeks of treatment.

The European Medicines Agency has deferred the obligation to submit the results of studies with Axhidrox in one or more subsets of the paediatric population in condition, as per paediatric investigation plan (PIP) decision, for the granted indication (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Axhidrox has local effect, but systemic exposure does occur. The pharmacokinetics of Axhidrox was investigated in a pharmacokinetic study in 30 patients with primary axillary hyperhidrosis, with 3 different dose strengths, 0.5%, 1% and 2% (Phase 1b Study). With continuous application of Axhidrox once a day, the pharmacokinetic steady state of glycopyrronium was achieved between Day 7 and 14 of treatment. The pharmacokinetics on Day 14 following administration of the 1% strength showed a mean T_{max} of about 4 hours, a mean (SD) AUC_{0-8h} of 128.61 (94.63) h*pg/mL and a maximal concentration of 24.39 (15.23) pg/mL. Total and maximum glycopyrronium exposure generally increased with dose from 4.3 mg to 17.3 mg glycopyrronium (corresponding to the 0.5%, 1% and 2% strength, respectively), with values being highly variable, due to the nature of the locally applied locally acting drug.

Distribution

The volume of distribution was investigated in two studies after i.v. administration, in adults and children and corresponds to that of total body water. It was 0.64 L/kg in adults and 1.4 L/kg in children.

Biotransformation

No clinical studies were performed to assess the biotransformation of glycopyrronium in humans. Therefore, neither the metabolites nor the metabolic pathway are known.

Elimination

After a single local application of Axhidrox, quantifiable plasma levels of glycopyrronium were detectable for at least 24 hours.

After intravenous administration of radioactively labelled glycopyrronium to adults, the glycopyrronium was mainly excreted via the kidneys (85%) and to a lesser extent (< 5%) via the bile. This mostly took place in unchanged form. The clearance of glycopyrronium in patients with severe renal dysfunction is considerably delayed.

5.3 Preclinical safety data

Non-clinical data reveal no special risk for humans using Axhidrox based on standard animal studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

The systemic exposure in patients from the clinical Phase 1b study was 4-fold or 7-fold lower (based on C_{max} or AUC, respectively) when compared to exposure data in minipigs following daily application of 2% GPB cream for 7 days. No adverse event was seen, when treating minipigs with 2% GPB cream.

Glycopyrronium was negative in a battery of genetic toxicology studies and was not carcinogenic when topically applied to rats daily for up to 24 months.

Since the systemic exposure of glycopyrronium following dermal application in patients is low with mean (SD) in AUC0-8h of 128.61 (94.63) h*pg/mL and a maximal concentration of 24.39 (15.23) pg/mL), no risk for systemic toxicity and reproduction and development is expected.

In male rats, glycopyrronium following subcutaneous administration showed no effect on fertility, while in females, a reduction in both the rate of conception and the survival rate of the offspring was noticed during the weaning phase. Based on the low systemic exposure following topical application of Axhidrox, these findings are not considered relevant for the human dermal use. No or limited placenta transfer was observed in pregnant mice, rabbits, dogs and humans. Glycopyrronium and its metabolites distributed into milk from lactating rats and generally reached higher concentrations in milk when compared with those observed in plasma (up to 11.3 times). However, systemic exposure of glycopyrronium following dermal application in patients is low and consequently, enriched concentrations in the milk would also still be low with no pharmacologic or toxicologic concern.

In vitro studies conducted with Axhidrox do not show any eye irritation potential. Based on the very low potential of sensitization in mice, a sensitizing effect in humans cannot be completely ruled out in very rare cases.

No phototoxicity is expected by application of Axhidrox.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (E1519)

Propylene glycol (E1520)

Cetostearyl alcohol

Citric acid (E330)

Glycerol monostearate 40–55

Macrogol 20 glycerol monostearate

Sodium citrate (E331)

Octyldodecanol

Water, purified

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

After first actuation, the medicinal product may be used for a maximum of 12 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Multidose container consisting of a container part (pouch laminate of LDPE, PET and aluminium encased in white rigid polypropylene bottle) and a pump part and its cap (both of white polypropylene).

Pack size: One container containing 50 g cream corresponding to 124 actuations or 31 treatments in both armpits.

In order not to exceed the number of treatments per container, the user is invited to mark the number in the table on the outer carton.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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22767 Hamburg

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8 MARKETING AUTHORISATION NUMBER(S)

PL 47848/0056

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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